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ABSTRACT

CKD prevalence estimation is central to CKD management and prevention planning at the population level. This study estimated CKD prevalence in the European adult general population and investigated international variation in CKD prevalence by age, sex, and presence of diabetes, hypertension, and obesity. We collected data from 19 general-population studies from 13 European countries. CKD stages 1–5 was defined as eGFR<60 ml/min per 1.73 m^2, as calculated by the CKD-Epidemiology Collaboration equation, or albuminuria >30 mg/g, and CKD stages 3–5 was defined as eGFR<60 ml/min per 1.73 m^2. CKD prevalence was age- and sex-standardized to the population of the 27 Member States of the European Union (EU27). We found considerable differences in both CKD stages 1–5 and CKD stages 3–5 prevalence across European study populations. The adjusted CKD stages 1–5 prevalence varied between 3.31% (95% confidence interval [95% CI], 3.30% to 3.33%) in Norway and 17.3% (95% CI, 16.5% to 18.1%) in northeast Germany. The adjusted CKD stages 3–5 prevalence varied between 1.0% (95% CI, 0.7% to 1.3%) in central Italy and 5.9% (95% CI, 5.2% to 6.6%) in northeast Germany. The variation in CKD prevalence stratified by diabetes, hypertension, and obesity status followed the same pattern as the overall prevalence. In conclusion, this large-scale attempt to carefully characterize CKD prevalence in Europe identified substantial variation in CKD prevalence that appears to be due to factors other than the prevalence of diabetes, hypertension, and obesity.

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CKD reduces lifespan significantly.[1] Individuals with CKD have an increased risk of cardiovascular disease and may develop ESRD.[1,2] Fortunately, the development of these complications can be delayed or prevented.[1]

CKD prevalence estimation is central to CKD management and prevention planning at the population level.[3] Identification of countries with a relatively low or high CKD prevalence will guide the medical community and policy makers where to focus prevention and disease management strategies. To date, international comparisons have been hampered by differences in national age and sex distributions and in definitions of CKD.[4] Moreover, prevalence estimates are influenced by the use of different creatinine determination methods.[5,6]

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Table 1. Description of included studies and study sampling methods

Country	Region(s)/Cities	Study	Age Range	Sampling Frame	Sample Selection	Response (%)	Representativeness[b]
Finland	All	FINRISK	25–74	Population register	Age and sex stratified sample	70	Yes
France	Bordeaux, Dijon and Montpellier	Three City	65+	Electoral rolls	Random sample of noninstitutionalized individuals	37	Yes
	Lille, Bas-Rhin and Haute-Garonne	MONALISA	35–74	Electoral rolls	Age and sex stratified random sample	51	Yes
Germany	South	ActiFE	65–91	Population register	Age and sex stratified random sample of noninstitutionalized individuals	20	Yes
	Southwest	ESTHER	50–74	General practitioners lists	Recruitment during biannually health examination for older adults	Not given	Yes[c]
	Northeast	SHIP	20–79	Population registers	Two stages: (*1*) Stratification based on N. of residents per municipality (*2*) Age and sex stratified random sample selection per community	69	Yes
Ireland	All	SLAN	45+	Postal residential lists	Age and urban/rural location and social class stratified sample	66	Yes[d]
Italy	Northeast	INCIPE	40+	General practitioners lists	Random selection of participants from 62 random selected practices	62	Yes
	Central	MATISS	20–79	Electoral rolls	Age and sex stratified random sample of four municipalities	60	Yes
	South	VIP	25–74	Electoral rolls	Age and sex stratified random sample	72	Yes
Netherlands	North	LifeLines	20+	General practitioners lists	Two stages: (*1*) All subjects aged 25–50 years registered with general practitioner[a] (*2*) Family members of first sample	Not given	Yes
	Groningen	PREVEND	28–75	Population register	Three stages: (*1*) All inhabitants of city (*2*) Selection of subjects based on albuminuria level (*3*) Correction for oversampling of albuminuria	48	Yes
Norway	Central	HUNT	20+	Census data	All residents in region	71	Yes
Poland	All	PolSenior	65+	Population register	Three stages: (*1*) Stratification based on N. of residents per municipality (*2*) Stratification based on streets/towns (*3*) Age stratified random sample	42	Yes
Portugal	All	PREVADIAB	20–79	Universal health card (held by 99% of population)	Two stages: (*1*) Age and sex stratified sample (*2*) Correction for unintentional oversampling of elderly females	84	Yes[d]

Table 1. Continued

Country	Region(s)/Cities	Study	Age Range	Sampling Frame	Sample Selection	Response (%)	Representativeness[b]
Spain	All	EPIRCE	20+	Census data	Age and sex and habitat stratified random sample	43	Yes
Sweden	Uppsala	PIVUS	70–70	Population register	Random selection of all (70-year-old) residents	50	n/a
Switzerland	Southwest	Bus Santé	35–74	Population register	Age and sex stratified sample	62	Yes[e]
UK	All	MRC	75+	General practitioners lists	Patients registered in a representative sample of general practices	73	Yes

Study acronyms: FINRISK, Finland Cardiovascular Risk Study; MONALISA, MOnitoring NAtionaL du rISque Arteriel; ActiFE Ulm, Activity and Function in the Elderly in Ulm study; ESTHER, Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten THerapie chronische ERkrankungen in der älteren Bevölkerung; SHIP, Study of Health in Pomerania; SLAN, Survey of Lifestyle and Attitudes & Nutrition in Ireland; INCIPE, Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints; MATISS, Malattie cardiovascolari ATerosclerotiche Istituto Superiore di Sanita; VIP, Valle dell'Imo Prevenzione; LifeLines, LifeLines Cohort and Study Biobank; PREVEND, Prevention of Renal and Vascular End-stage Disease; HUNT, Nord-Trøndelag Health Study; PolSenior, Medical, psychologic, sociological and economical aspects of aging of people in Poland; PREVADIAB, Prevalence of Diabetes and Risk Factors in Portugal; EPIRCE, Estudio Epidemiológico de la Insuficiencia Renal en España; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors Study; MRC, Medical Research Council trial of assessment and management of older people in the community.

[a]LifeLines additionally included participants which actively volunteered to participate; however, the vast majority of the LifeLines cohort presented in this paper was recruited through their general practitioner.

[b]Representative = age and sex distribution of the study sample is nonsignificantly different from regional/national age and sex distribution.

[c]Under sampling of males in age group 55–59 years, the remaining age ranges were nonsignificantly different from Saarland population of 2000.

[d]After the study population was weighted to census data, there was no significant difference.

[e]Under sampling of age group 35–39 years, the remaining age ranges were nonsignificantly different from the Geneva population of 2005.

Because diabetes, hypertension, and obesity are important risk factors for CKD,[2] the prevalence of these diseases should be taken into account when comparing CKD prevalence. Whether disparities in CKD prevalence are explained by these risk factors will guide policy makers to focus on secondary or primary prevention.

Therefore the purpose of our study was (*1*) to estimate the CKD prevalence in the adult general population across Europe, and (*2*) to investigate variation in prevalence across countries by age, sex, and the presence of diabetes, hypertension, and obesity. We collected data from 19 general population-based studies from 13 European countries and estimated CKD prevalence using one definition of CKD.

RESULTS

Study Characteristics

Study Populations

We included data from 19 general population-based studies from 13 European countries (Table 1). Table 2 presents study population characteristics and laboratory methods for the nine studies using isotope dilution mass spectrometry (IDMS) traceable creatinine, which included a large spectrum of the adult population (≥45 years). Supplemental Appendix 1, Table 1 presents these data for all 19 studies for subjects aged ≥65 years.

Representativeness of Study Populations

Thirteen (68%) studies used a population register/electoral rolls as sampling frame to identify eligible participants (Table 1). Four (21%) studies used general practitioner lists and two studies used other sampling frames. The response varied between 20% and 84%, with two studies not providing a response percentage. The response was at least 60% in ten (59%) studies. Five studies independently performed nonresponse analyses to test representativeness of study populations.[7–11] Two studies (Survey of Lifestyle and Attitudes & Nutrition in Ireland, and Prevalence of Diabetes and Risk Factors in Portugal) weighted the study population to correct for oversampling of females and older individuals in comparison to their respective national population. In the nine studies that covered the entire adult population, the age and sex distribution was not significantly different from the age and sex distribution of their respective target populations (Table 1).

Creatinine Measurements

Serum creatinine was determined by Jaffe assays in the majority of studies (n=14; 74%) and four studies used enzymatic assays (21%). The Medical Research Council trial of assessment and management of older people in the community study used both Jaffe and enzymatic assays, with the majority of laboratories using Jaffe assays. IDMS standardization was used in 13 studies (68%), of which the CKD prevalence estimates are presented in the body of this paper; the CKD prevalence estimates of

Table 2. Study population characteristics and laboratory methods of IDMS studies covering age range 45–74 years

Country	Finland	Germany	Italy	Netherlands	Norway	Spain	Italy	Ireland	Switzerland
Study	FINRISK	SHIP	MATISS	LifeLines	HUNT	EPIRCE	INCIPE	SLAN	Bus Santé
Age range	Ages 20+						Ages 45+		
N study population	4228	4308	3780	94,133	65,252	2746	3868	1160	4748
Sample collection years	2007	1997–2001	1993–1996	2007–2013	1995–1997	2004–2008	2006–2007	2007	2005–2008
Mean age, years (SD)	49.7 (12.5)	49.8 (16.4)	49.2 (14.1)	44.6 (12.5)	50.3 (17.3)	49.3 (16.3)	59.8 (11.4)	59.7(9.9)	58.4 (11.0)
Females (%)	54.3	50.9	48.8	58.7	53.22	58.2	52,0	56,0	48.9
DM (%)	8.4	11.0	5.1	2.4	3.4	10.3	7.42	7.7	4.2
HT (%)	43.3	52.5	15.6	18.2	43.7	41.2	35.89	57,0	23,0
Smokers (%)	18.8	30.3	27.6	18.8	29.2	25.3	15.32	18.3	13.6
Mean SBP, mmHg (SD)	132 (19)	136 (21)	140 (23)	126 (15)	138 (22)	131 (22)	138 (20)	140 (20)	127 (23)
Mean DBP, mmHg (SD)	79 (11)	83 (11)	85 (13)	74 (9)	80 (12)	79 (12)	85 (10)	82 (13)	76 (11)
Mean BMI (kg/m^2) (SD)	27.1 (4.9)	27.3 (4.8)	27.7 (4.5)	26.1 (4.3)	26.4 (4.10)	27.5 (5.3)	26.7 (5.2)	27.98 (4.58)	25.6(4.17)
ARB use (%)	n/a	1.7	n/a	n/a	n/a	5,0	n/a	n/a	n/a
ACEi use (%)	n/a	12.8	n/a	n/a	n/a	6.4	n/a	n/a	n/a
ACEi/ARB use (%)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Creatinine method	Enzymatic	Jaffe	Enzymatic	Enzymatic	Jaffe	Jaffe	Jaffe	Jaffe	Jaffe
IDMS traceable creatinine?	Yes	Yes	Yes	Yes	Yes	Yes	Standardized	no	yes
Albuminuria method	n/a	Immunoassay	n/a	Immunoassay	Immunoassay	Immunoassay	Immunoassay	Bromocresol green	n/a
Mean eGFR by CKD-EPI (SD)	89.5 (15.0)	82.2 (17.0)	100.4 (14.8)	96.5 (15.0)	97.6 (19.5)	86.6 (18.0)	85.7 (16)	80.7(16.9)	89.5(13.4)
Mean eGFR by MDRD (SD)	86.9 (15.0)	79.4 (15.1)	103.4 (19.7)	93.4 (17.1)	100.1 (24.2)	84.1 (17.7)	87.8 (20)	81.1(18.3)	90.6(15.8)
Median ACR mg/g (25–75 p)	n/a	8.4 (5.1–17.3)	n/a	2.2 (1.3–4.2)	10.3 (7.4–14.5)	4.6 (2.5–8.6)	Available in dip+	9.45(4.46–18.42)	n/a

DM, diabetes mellitus; HT, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; ARB, angiotensin receptor blockers; ACEi, angiotensin-converting enzyme inhibitors; ARB/ACEi, use of either ARB or ACEi; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; ACR, albumin-to-creatinine ratio; FINRISK, Finland Cardiovascular Risk Study; n/a, not applicable; MATISS, Malattie cardiovascolari ATerosclerotiche Istituto Superiore di Sanita; LifeLines, LifeLines Cohort and Study Biobank; HUNT, Nord-Trøndelag Health Study; EPIRCE, Estudio Epidemiológico de la Insuficiencia Renal en España; INCIPE, Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints; dip+, ACR was calculated in participants with positive results on the dipstick test for proteinuria; SLAN, Survey of Lifestyle and Attitudes & Nutrition in Ireland.

studies using non–IDMS-standardized creatinine (n=6, 32%) are presented exclusively in Supplemental Appendix 1.

Albuminuria Measurements

Of the 11 studies that collected albuminuria data, ten (91%) used immunoassays to measure urinary albumin. Two studies (18%) used dipsticks to assess albuminuria presence, which was confirmed by immunoassay in the Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints study.

CKD Stage 1–5 Prevalence

Adult Population

Prevalence estimates were adjusted to the age and sex distribution of the population of the 27 Member States of the European Union (EU27) in 2005[12] to correct for differences in national age and sex distributions. The adjusted CKD stages 1–5 prevalence in the adult population, including subjects aged 20–74 years, for studies using IDMS-standardized creatinine varied between 3.31% (95% confidence interval [95% CI], 3.30 to 3.33) in Norway and 17.3% (95% CI, 16.5 to 18.1) in the Northeast German Study of Health in Pomeranzia (SHIP) study (Supplemental Appendix 1, Figure 1).

Supplemental Appendix 1, Table 2 shows the unadjusted and adjusted CKD stages 1–5 prevalence in the adult population, for both IDMS and non-IDMS studies. For studies using non–IDMS-standardized creatinine, the unadjusted and adjusted CKD stages 1–5 prevalence in the adult population is graphically presented in Supplemental Appendix Figure 1.

Across Age Strata

Figure 1 shows the geographic variation in the adjusted CKD stages 1–5 prevalence in the population aged 45–74 years, for studies using IDMS-standardized creatinine. Figure 2A shows this adjusted CKD stages 1–5 prevalence, including 95% CI. This prevalence varied between 6.3% (95% CI, 6.0 to 6.5) in Norway and 25.6% (95% CI, 23.7 to 27.5) in the Northeast German SHIP study.

The prevalence of CKD stages 1–5 for age categories 20–44 years, 45–64 years, 65–74 years, and 75–84 years is shown in Supplemental Appendix 1, Figure 2, 1–4, separately for studies using IDMS and non–IDMS-standardized creatinine assays. The CKD stages 1–5 prevalence was lowest in the age group 20–44 years and increased with every consecutive age group.

Across Risk Strata

Figure 2, B–D presents the CKD stages 1–5 prevalence in the population aged 45–74 years of studies using IDMS-standardized creatinine, stratified by diabetic, hypertension, and obesity status. The variation in CKD stages 1–5 prevalence stratified by risk factors followed the pattern of the overall adjusted prevalence across regions. Supplemental Appendix 1, Figure 1, B–D, show this same pattern in the adult population, separately for studies using IDMS- and non–IDMS-standardized creatinine.

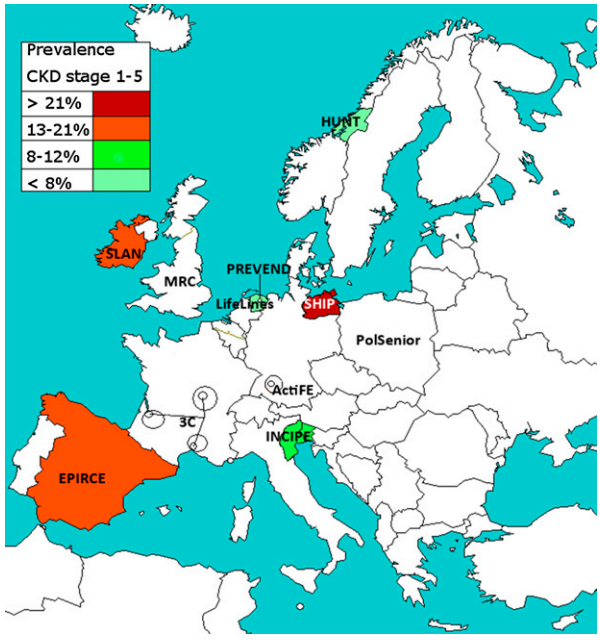

Figure 1. Adjusted CKD stages 1–5 prevalence in the population aged 45–74 years, in IDMS studies. Prevalence was age- and sex-adjusted to the EU27 population of 2005. The study names in uncolored regions are studies which used non–IDMS-standardized creatinine or studies which recruited subjects aged ≥50 years: the CKD prevalence results of these studies are shown in Supplemental Appendix 1. 3C, Three City Study; ActiFE, Activity and Function in the Elderly in Ulm study; EPIRCE, Estudio Epidemiológico de la Insuficiencia Renal en España; HUNT, Nord-Trøndelag Health Study; INCIPE, Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints; LifeLines, LifeLines Cohort and Study Biobank; MRC, Medical Research Council trial of assessment and management of older people in the community; PolSenior, Medical, psychological, sociological and economical aspects of aging of people in Poland; PREVEND, Prevention of Renal and Vascular End-stage Disease; SLAN, Survey of Lifestyle and Attitudes & Nutrition in Ireland.

CKD Stage 3–5 Prevalence

Adult Population

Supplemental Appendix 1, Figure 3 shows the CKD stages 3–5 prevalence including 95% CI for the adult population, separately for IDMS and non-IDMS studies. This CKD stages 3–5 prevalence varied between 1.0% (95% CI, 0.7 to 1.3) in the Italian Malattie cardiovascolari ATerosclerotiche Istituto Superiore di Sanita study and 5.9% (95% CI, 5.2 to 6.6) in the Northeast German SHIP study.

Supplemental Appendix 1, Table 2 shows the unadjusted and adjusted CKD stages 3–5 prevalence in the adult population, for both IDMS and non-IDMS studies. For studies using non–IDMS-standardized creatinine, the unadjusted and adjusted CKD stages 3–5 prevalence in the adult population

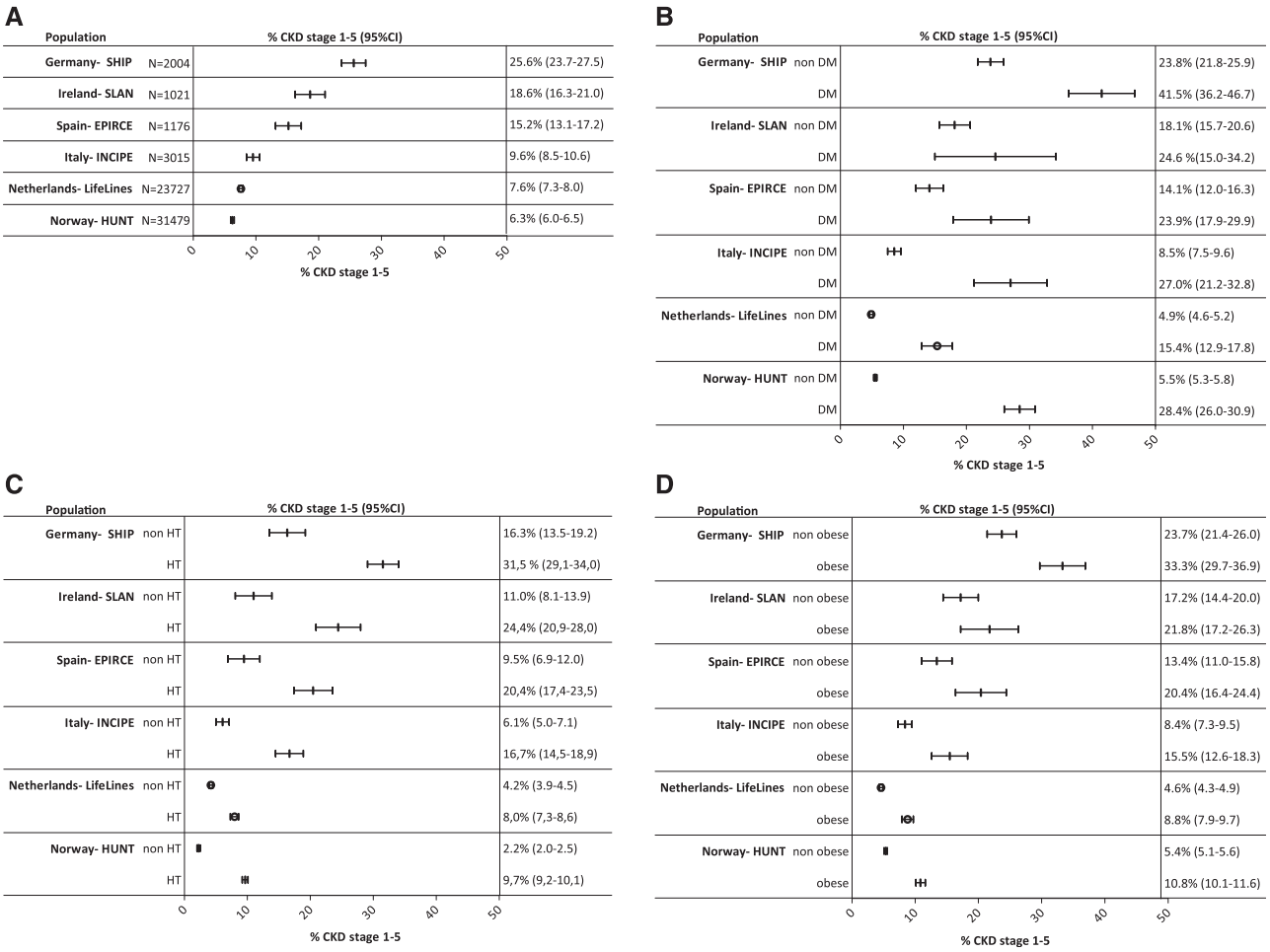

Figure 2. (A) Adjusted CKD prevalence stages 1–5 (95% CI) in the population aged 45–74 years, in IDMS studies. (B) CKD prevalence stages 1–5 (95% CI) in the population aged 45–74 years, in IDMS studies, by diabetic status. (C) CKD prevalence stages 1–5 (95% CI) in the population aged 45–74 years, in IDMS studies, by hypertensive status. (D) CKD prevalence stages 1–5 (95% CI) in the population aged 45–74 years, in IDMS studies, by obesity status. Prevalence was age- and sex-adjusted to the EU27 population of 2005. N, the number of study subjects aged 45–74 years with creatinine and albuminuria measurement. Studies not covering the entire age range are not included in this figure. DM, diabetes mellitus; EPIRCE, Estudio Epidemiológico de la Insuficiencia Renal en España; HUNT, Nord-Trøndelag Health Study; HT, hypertension; INCIPE, Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints; LifeLines, LifeLines Cohort and Study Biobank; SLAN, Survey of Lifestyle and Attitudes & Nutrition in Ireland; Θ, studies using enzymatic method; I studies using Jaffe method.

is graphically presented in Supplemental Appendix 1, Figure 3A.

Across Age Strata

Figure 3 shows the geographic variation of the adjusted CKD stages 3–5 prevalence in the population aged 45–74 years, for studies using IDMS-standardized creatinine. Figure 4A shows the overall adjusted CKD stages 3–5 prevalence in these studies, including 95% CI. This CKD prevalence varied between 1.7% (95% CI, 1.3 to 2.1) in the Swiss Bus Santé study and 11.5% (95% CI, 10.2 to 12.8) in the Northeast German SHIP study.

The prevalence of CKD stages 3–5 for age categories 20–44 years, 45–64 years, 65–74 years, and 75–84 years is shown in Supplemental Appendix 1, Figure 4, 1–4, separately for studies using IDMS and non–IDMS-standardized creatinine assays. The CKD stages 3–5 prevalence was lowest in the youngest age group and increased with every consecutive age group.

Across Risk Strata

Figure 4, B–D presents the CKD stages 3–5 prevalence in the population aged 45–74 years of studies using IDMS-standardized creatinine, stratified by diabetic, hypertension, and obesity status. The variation in CKD stages 3–5 prevalence stratified by risk factor followed the pattern of the overall adjusted prevalence across regions. Supplemental Appendix 1, Figure 3, B–D, show this same pattern in the adult population, separately for studies using IDMS- and non–IDMS-standardized creatinine.

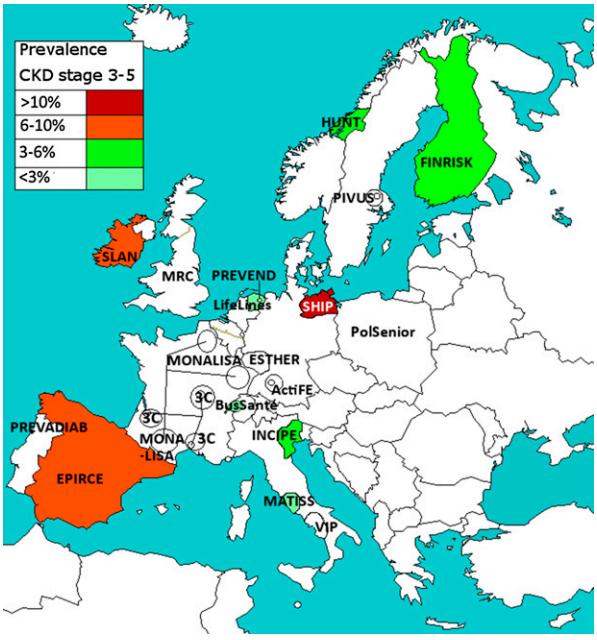

Figure 3. Adjusted CKD stages 3–5 prevalence in the population aged 45–74 years, in IDMS studies. Prevalence was age- and sex-adjusted to the EU27 population of 2005. The study names in uncolored regions are studies which used non–IDMS-standardized creatinine or studies which recruited subjects aged ≥50 years; the CKD prevalence results of these studies are shown in Supplemental Appendix 1. 3C, Three City Study; ActiFE, Activity and Function in the Elderly in Ulm study; EPIRCE, Estudio Epidemiológico de la Insuficiencia Renal en España; ESTHER, Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten THerapie chronische ERkrankungen in der älteren Bevolkerung; FINRISK, Finland Cardiovascular Risk Study; HUNT, Nord-Trøndelag Health Study; INCIPE, Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints; LifeLines, LifeLines Cohort and Study Biobank; MATISS, Malattie cardiovascolari ATerosclerotiche Istituto Superiore di Sanita; MONA LISA, MOnitoring NAtionaL du rISque Arterie; MRC, Medical Research Council trial of assessment and management of older people in the community; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors Study; PolSenior, Medical, psychological, sociological and economical aspects of aging of people in Poland; PREVADIAB, Prevalence of Diabetes and Risk Factors in Portugal; PREVEND, Prevention of Renal and Vascular End-stage Disease; SLAN, Survey of Lifestyle and Attitudes & Nutrition in Ireland; VIP, Valle dell'Irno Prevenzione

DISCUSSION

Our study suggests a substantial variation in CKD prevalence across Europe. Stratification by risk factors further suggests that this variation in CKD prevalence is remarkably consistent across high- and low-risk populations, implying that the difference in overall prevalence of CKD is at least in part due to other factors than the prevalence of diabetes, hypertension, and obesity in the general population.

Global Perspective

Regional differences in CKD prevalence have been documented around the world, even when comparing age- and sex-adjusted prevalence estimates using standardized creatinine methods. For example, in the adult general population of the United States, the adjusted CKD stages 3–5 prevalence varied from 4.8% in the Northeast to 11.8% in the Midwest.[13] In contrast, in China the adjusted CKD stages 3–5 prevalence showed lower prevalence estimates, from 1.1% in East China to 3.8% in Southwest China.[14] This variation is similar to that in Europe, where the adjusted CKD stages 3–5 prevalence varied from 1.0% to 5.9%. The adjusted CKD stages 1–5 prevalence in China showed larger variation, from 6.7% in South China to 18.3% in Southwest China.[10] In Europe, this adjusted CKD stages 1–5 prevalence varied from 3.3% to 17.3%.

Explanatory Factors in Europe

There are many factors which potentially contribute to the observed differences in CKD prevalence across countries and regions. We argue that these differences are possibly due to true differences in the prevalence of CKD as well as to heterogeneity of studies. In the following we will discuss five possible explanations.

Human and Environmental Factors

Dietary habits across European regions vary substantially.[15] Dietary protein intake is known to influence serum creatinine and thus eGFR.[16,17] This may not only be an artifact, but also a true effect, because studies have shown that protein-rich diets are associated with accelerated eGFR decline.[18] Also, the Mediterranean diet has been suggested to reduce the risk of development of CKD.[19] Therefore, regional differences in dietary habits could lead to a difference in observed CKD prevalence through both a direct effect on serum creatinine and through reno-damaging or reno-protective influences. Additionally, there are multiple other factors associated with CKD prevalence, such as smoking, physical activity,[20] socioeconomic status,[21] and birth weight.[22] These factors may vary between regions and may therefore contribute to the observed CKD prevalence variation.

Public Health Policies

European regions differ greatly with regard to healthcare policies.[23] Public health initiatives may both prevent diseases and their complications by primary and secondary prevention, respectively.[24] National and regional public health initiatives may therefore contribute to differences in the prevalence of underlying causes of CKD, like diabetes, hypertension, and obesity, as well as to the prevalence of CKD itself.

The consistently higher prevalence of CKD in high- compared with low-risk groups implies that the focus of public health initiatives should, indeed, lie with prevention of CKD in patients with underlying diseases. However, the remarkable consistency of international variation in CKD prevalence, irrespective of the presence of risk factors, emphasizes that the focus of public health initiatives should also lie with primary

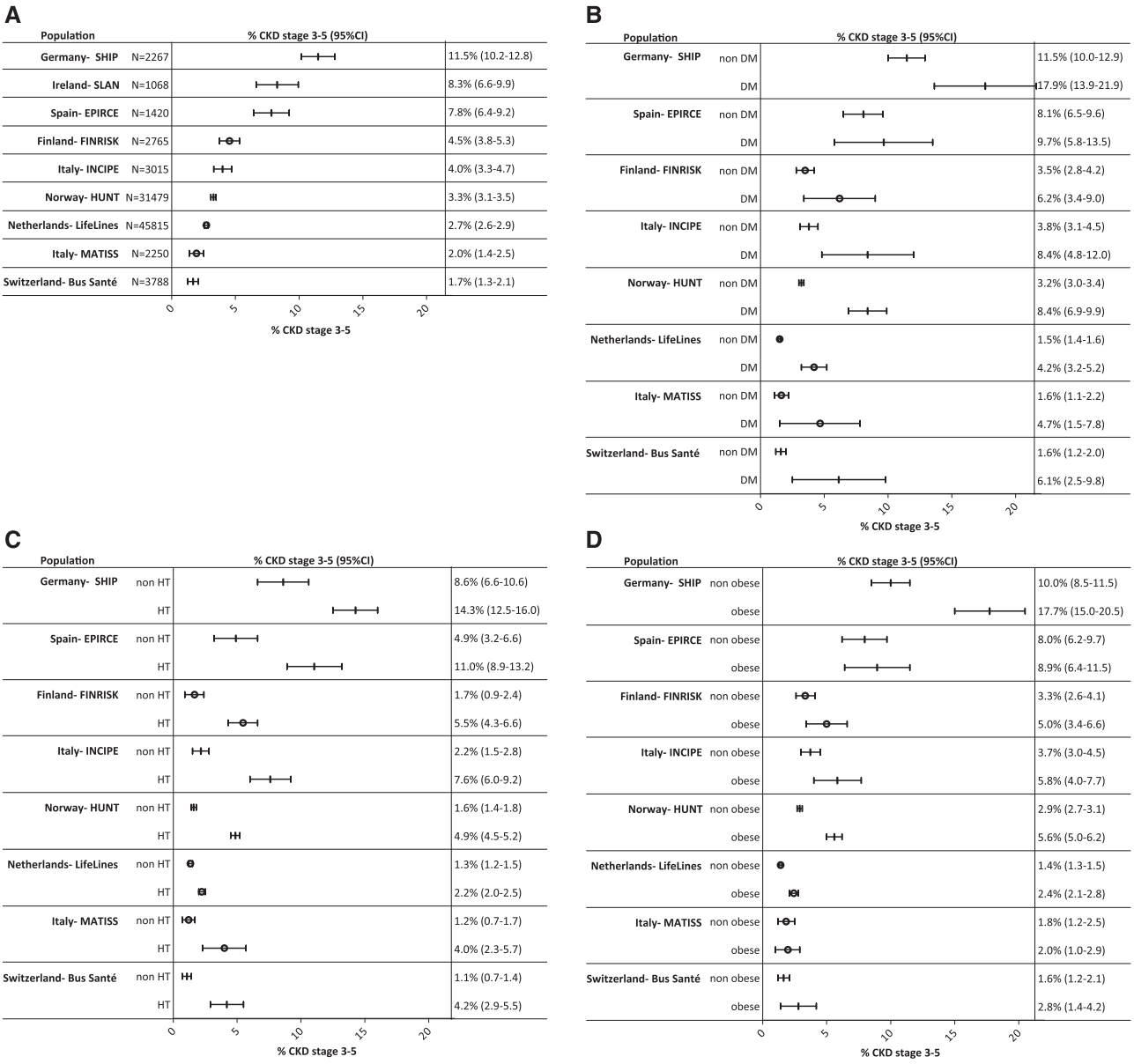

Figure 4. (A) Adjusted CKD prevalence stages 3–5 (95% CI) in the population aged 45–74 years, in IDMS studies. (B) CKD prevalence stages 3–5 (95% CI) in the population aged 45–74 years, in IDMS studies, by diabetic status. (C) CKD prevalence stages 3–5 (95% CI) in the population aged 45–74 years, in IDMS studies, by hypertensive status. (D) CKD prevalence stages 3–5 (95% CI) in the population aged 45–74 years, in IDMS studies, by obesity status. Prevalence was age- and sex-adjusted to the EU27 population of 2005. N, the number of study subjects aged 45–74 years with creatinine measurement. Studies not covering the entire age range are not included in this figure. DM, diabetes mellitus; EPIRCE, Estudio Epidemiológico de la Insuficiencia Renal en España; FINRISK, Finland Cardiovascular Risk Study; HUNT, Nord-Trøndelag Health Study; INCIPE, Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints; LifeLines, LifeLines Cohort and Study Biobank; MATISS, Malattie cardiovascolari ATerosclerotiche Istituto Superiore di Sanita. Θ studies using enzymatic method; I studies using Jaffe method.

prevention of CKD, through the promotion of a healthy lifestyle in the entire population.

Genetic Factors

In studies which collected ethnicity data, almost all participants were white. However, even within the white European populations there are substantial genetic differences.[25] Studies have shown that the development of CKD and the incidence of RRT are associated with multiple genetic loci.[26,27] The regional differences in CKD prevalence could therefore be influenced by genetic differences across the various regions. This has been shown for the geographic pattern in the

prevalence of RRT for IgA nephropathy.[28] Because 7.1% of all RRT is provided for hereditary nephropathies (European Renal Association–European Dialysis and Transplant Association Registry, unpublished data), it is to be expected that some of the variation in CKD prevalence is also due to genetic differences.

Heterogeneity in Laboratory Methods

In addition to reflecting true differences in CKD prevalence, our results may also vary due to the heterogeneity of methodology used to measure creatinine[5] and albuminuria,[29] including differences in assays but also in handling and storage conditions (*e.g.*, duration as well as number of freeze and thaw cycles until analysis).[29,30]

Differences in creatinine assays will likely contribute to the variation in CKD prevalence, as most Jaffe assays overestimate serum creatinine.[5] The resulting bias may vary depending on the creatinine concentration, specific assay, manufacturer, and calibration material used.[31,32] Fortunately, the IDMS calibration standardization has reduced the bias and improved the interlaboratory comparability.[5,32] Despite the use of IDMS standardization, some interlaboratory variability still exists,[31] being lowest in IDMS-standardized enzymatic assays.[5] Notably, our study shows substantial differences in CKD stages 3–5 prevalence across studies using enzymatic IDMS-standardized assays. In these studies, the adjusted CKD stages 3–5 prevalence in the age group 65–74 years varied from 4.8% in central Italy to 11.4% in Finland.

Moreover, CKD stages 1–5 prevalence may additionally be influenced by albuminuria assays.[29] As recommended by Kidney Disease Improving Global Outcomes (KDIGO), urinary albumin was measured by immunoassays in 91% of studies and we used urinary albumin-to-creatinine ratio for the definition of CKD.[1] Importantly, there is no standardization available to enhance comparability of immunoassays across laboratories.[29]

Heterogeneity in Study Populations

Finally, differences in prevalence may have resulted from differences in population sample selections. As in the United States, CKD prevalence in Europe may have changed over time, and this might explain some of the observed differences.[33] Nevertheless, we found both high and low CKD prevalence in older and in more recent studies. For example, in studies performed in the period 2005–2010 using the IDMS-standardized Jaffe method, the adjusted CKD stages 3–5 prevalence in the age group 65–74 years ranged from 4.1% in Switzerland to 20.8% in South Germany. This suggests that differences in time periods cannot fully explain the observed differences in CKD prevalence.

Although all studies were designed to be representative of the respective regional or national general population, their sample selections varied substantially as outlined in Table 1. Sample selection methods influence the coverage of the population investigated and influence the response, which both influence the ultimate representativeness of the sample.[34,35] We have checked the representativeness of the included studies by comparing the age and sex distribution of the study populations to the relevant census data. Although overall the study populations appear to be representative for the age and sex distribution of their target population, we cannot exclude a selection bias based on unmeasured factors, such as the presence of (unmeasured) comorbidities.

Studies with high response are less likely to suffer from nonresponse bias, yet the impact of nonresponse bias on representativeness is not solely determined by the response.[34] Even with low response a sample may be highly representative by chance alone. To date, there is no validated method to measure the influence of nonresponse bias on the representativeness of study results.[34,36] However, nonresponse analyses can provide some insight into the likely direction of a possible nonresponse bias.[34] All nonresponse analyses performed by the individual studies suggested that recruited participants were similar or healthier in comparison to nonparticipants.[7–11] This might have led to an underestimation of the true CKD prevalence in these studies.

Strengths and Limitations

The new European CKD Burden Consortium enabled this first large-scale study to describe CKD prevalence across Europe. The comparability of CKD prevalence across studies was increased by using the same definition based on one eGFR equation. Additionally, we only compared studies using IDMS-standardized creatinine to increase interlaboratory comparability of creatinine results. Moreover, the comparability of study populations across European countries was enhanced by removing the influence of differences in national age and sex distributions through age and sex standardization to the EU27 population.[12] Finally, to avoid the influence of international differences in the prevalence of diabetes, hypertension, and obesity, we determined CKD prevalence in subgroups with and without these risk factors.

There are also limitations to this study. First, the prevalence of CKD might have been slightly overestimated using single creatinine and albuminuria measurements. However, this will not have influenced the variation of CKD prevalence across studies, as all estimations will be equally affected. Ethnicity status was not included in the eGFR equation because this was not available for all studies, which might have led to a slight overestimation of CKD prevalence in some studies. However, in studies which did collect ethnicity data, at least 96% were white; therefore, the expected impact on the overall prevalence estimation is negligible. Other limitations relate to the heterogeneity of included studies with regard to laboratory methods and sample selection. This heterogeneity might have influenced the variation of CKD prevalence as discussed. The first may be solved by central measurement of serum creatinine and albuminuria in a reference laboratory. The effect of response, however, is inherent to population surveys and cannot be avoided.

In conclusion, this is the first study which carefully characterizes CKD prevalence across Europe. Our results suggest

substantial variation in CKD prevalence across population samples in Europe. These differences are possibly due to true differences in the prevalence of CKD as well as to heterogeneity of the laboratory and sample selection methods. The effect of the variation in European regions with regard to human and environmental factors, public health policies, and genetics on CKD prevalence needs further investigation.

Our results may be used to guide future projections of the CKD burden in Europe and thereby help estimate the growing demand for CKD services that the ageing population will likely create. Our results are also a first step in monitoring the impact of strategies designed to reduce the burden of CKD in Europe. This monitoring may assist the medical community and policy makers in the further development of these strategies.

CONCISE METHODS

Data Collection

Study Selection

We first systematically searched scientific publications, to identify European studies with data on CKD prevalence in the general population (details described in Supplemental Appendix 2).[37] Additionally, the representatives of national kidney foundations, renal registries, and expert nephrologists in 39 European countries were asked to provide contact details for any relevant unpublished studies. Studies were included if they were designed to select a representative sample of the adult general population and CKD prevalence could be calculated. Studies that ended recruitment prior to 1996 were excluded. Eligible studies were invited to participate in an online questionnaire, assessing general study information (*e.g.*, period of participant inclusion), collected data, and regional healthcare system characteristics. Answers regarding collected data and healthcare system characteristics are shown in Supplemental Appendix 2, Tables 1 and 2, respectively. Finally, studies that agreed to contribute data were sent a statistical analysis syntax to collect aggregated data. All studies were approved by local ethical committees and all participants gave consent.

All studies which contributed data were included in the European CKD Burden Consortium. The European CKD Burden Consortium, including nephrologists and epidemiologists, was established to characterize CKD prevalence and progression of CKD across Europe.

Collected Data

Data were collected for the total study population and for subgroups by age ($\leq$>65 years), sex, and by diabetes, hypertension, and obesity (body mass index $\geq$30 kg/m^2) status. For the continuous variables age, systolic and diastolic blood pressure, body mass index, eGFR, and urinary albumin-to-creatinine ratio, we collected the mean (SD) and median (25th and 75th percentiles). In addition, we collected the following factors known to influence kidney function: the proportion of current smokers and individuals using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Furthermore, we collected the laboratory methods for the measurement of serum creatinine and detection of albuminuria. Serum creatinine was measured by a Jaffe or enzymatic method, both of which can be standardized to IDMS.[32] Diabetes was defined as self-reported diabetes and/or the use of glucose lowering medication. Hypertension was defined as a systolic blood pressure of $\geq$140 mmHg, a diastolic blood pressure of $\geq$90 mmHg, or the use of antihypertensive drugs.

Definition of CKD

1. CKD stages 1–5: eGFR<60 ml/min per 1.73 m^2 calculated by the CKD-Epidemiology Collaboration equation[1,38] and/or uACR$\geq$30 mg/g.

2. CKD stages 3–5: eGFR<60 ml/min per 1.73 m^2 calculated by the CKD-Epidemiology Collaboration equation.

These definitions were based on the KDIGO practice guideline.[1] As no studies repeated measurements after three months, the chronicity criterion (symptoms $\geq$3 months) was not applied to the definition.

Statistical Analyses

Normally distributed variables are presented as means with SD, and non-normally distributed data as medians with interquartile ranges. Dichotomous data are given in percentages. The representativeness of study populations was tested by comparing the age and sex distribution of the study population to the distribution of the relevant regional/national population using the chi-squared test. The prevalence of CKD stages 1–5 and CKD stages 3–5 with 95% CI is presented as unadjusted rates and weighted averages using the age and sex distribution of the 2005 EU27 population.[12] To limit the influence of random variation, this adjustment was only applied to studies with a minimum of 100 participants per included age stratum. Consequently, (sub)groups with insufficient numbers were excluded from this adjustment. Additionally, we stratified study populations into the following age groups: 45–74, 20–44, 45–64, 65–74, and 75–84 years, and whenever possible adjusted for the effect of age within strata. The age-stratified CKD prevalence is given for the overall study population as well as by diabetic, hypertension, and obesity status.

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